Touzeau
86460

```
=> d his l3

     (FILE 'CA' ENTERED AT 14:32:40 ON 06 NOV 92)
L3            196 S (FACTOR VIII C OR F VIII C OR FVIIIC)/AB,BI

=> s l3 and (amino acid# or arginine# or glycine# or salt#)/ab,bi
        271295 AMINO/AB
       1169853 ACID#/AB
        186547 AMINO ACID#/AB
                  ((AMINO(W)ACID#)/AB)
        232340 AMINO/BI
       1316937 ACID#/BI
        156623 AMINO ACID#/BI
                  ((AMINO(W)ACID#)/BI)
         31637 ARGININE#/AB
         16353 ARGININE#/BI
         38701 GLYCINE#/AB
         27706 GLYCINE#/BI
        311352 SALT#/AB
        224837 SALT#/BI
L4           36 L3 AND (AMINO ACID# OR ARGININE# OR GLYCINE# OR SALT#)/AB,
                BI

=> s l4 and (detergent# or polymer#)/ab,bi
         37789 DETERGENT#/AB
         29513 DETERGENT#/BI
        301777 POLYMER#/AB
        450556 POLYMER#/BI
L5            4 L4 AND (DETERGENT# OR POLYMER#)/AB,BI

=> d 1-4 .beverly

L5   ANSWER 1 OF 4  COPYRIGHT 1992 ACS
AN   CA115(4):35559j
TI   Large-scale preparation of a highly purified solvent-
   detergent treated factor VIII concentrate
SO   Vox Sang., 60(3), 141-7
AU   Myers, Robert; Wickerhauser, Milan; Charamella, Leigh; Simon,
     Louise; Nummy, William; Brodniewicz-Proba, Teresa
PY   1991
AB   Large-scale adaptation of a recently reported glycine
     pptn. method for the prodn. of factor VIII (FVIII) conc. is
     described. Scaling up of the method required some modification
     including the addn. of Al(OH)3 to the glycine buffer to
     reduce the level of contaminating proteins in the final prepn. and
     the use of centrifugation to replace filtration by glass beads.
     Furthermore, the resultant product was virus inactivated by
     incorporation of the org. solvent and detergent technique.
     At industrial level, the modified method gave a good recovery of
     FVIII activity (230 IU/L plasma) with high purity (4 IU/mg protein).
     The final product, after virus inactivation and lyophilization,
     yielded 185 IU of FVIII activity per L of starting plasma and was
     considered to be suitable for clin. evaluation.

L5   ANSWER 2 OF 4  COPYRIGHT 1992 ACS
AN   CA106(26):219573e
TI   Separation of antifactor VIII:C antibodies, especially for use in
     the blood plasma purification of a type A hemophilic
SO   Eur. Pat. Appl., 15 pp.
AU   Belattar, Noureddine; Gulino, Danielle; Jozefonvicz, Jacqueline
AI   EP 86-401115  27 May 1986
PI   EP 203865  A1  3 Dec 1986
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PY 1986
AB Antifactor VIII:C antibodies are removed from blood plasma by using a polymer bearing the groups (SO3)x M (M = metal; x = valence of the metal), SO2Y or COY (Y = NHCHR1CO2R2; R1 = .alpha.-amino acid side chain; R2 = H, alkyl). The polymer is i.a. polystyrene or a polysaccharide. Thus, chlorosulfonylated polystyrene was hydrolyzed with 2 M NaOH to give polystyrene bearing SO3Na groups. The product was used to remove antifactor VIII:C antibodies from the plasma of a type A hemophilic patient, using extracorporeal circulation.

L5 ANSWER 3 OF 4 COPYRIGHT 1992 ACS
AN CA106(24):201672b
TI Interactions between derivatives of insoluble polystyrene and human antibodies to Factor VIII:C
SO Polym. Sci. Technol. (Plenum), 34(Polym. Med. 2), 127-37
AU Belattar, N.; Gulino, D.; Jozefonvicz, J.; Sultan, Y.
PY 1986
AB In order to obtain completely synthetic adsorbents mimicking the interaction FVIII:C-AntiVIII:C, crosslinked polystyrene was modified by various amino acids or by some of their derivs. The syntheses of the resins were achieved by a two step process:crosslinked polystyrene was first chlorosulfonated and subsequently amino acids were attached onto the polymer. Then, the in vitro removal of Anti VIII:C from hemophiliac's IgG was tested by measuring simultaneous adsorptions of either IgG or Anti VIII:C onto the polymer surfaces. Among the different resins, some of them relatively possess specificity towards Anti III:C as they can adsorb 60% of Anti VIII:C and only 16% of IgG from the starting material. Another ones unspecifically absorb Anti VIII:C as well as the overall IgG.

L5 ANSWER 4 OF 4 COPYRIGHT 1992 ACS
AN CA103(20):166144v
TI Purifying factor VIII complexes
SO Ger. Offen., 30 pp.
AU Saundry, Richard Howard; Savidge, Geoffrey Francis
AI DE 85-3504385 8 Feb 1985
PI DE 3504385 A1 14 Aug 1985
PY 1985
AB Blood coagulation factor VIII [9001-27-8] and its complexes were purified by adsorption on an insol. matrix consisting of a sulfate such as dextran sulfate [9042-14-2] and selective elution from the matrix. Tri-Na citrate [68-04-2] buffer (pH 6.2-7.3) with a content of 10M glycine, 2.14 mM CaCl2 and 0.5M NaCl at 4.degree. is a suitable elution medium for the purifn. of factor VIII complexes such as Factor VIII R:Ag, Factor VIII R:vWP (von Willebrand proteins) and factor VIII:C . Thus, an aq. soln. of dextran sulfate was added to pptd. and washed Sepharose 6B or 9B and cooled to 4.degree.. CNBr was added to the soln. at pH 10.6-11.3 (4 N NaOH soln.). The polymer was washed with 0.2M Na3BO3/0.5M NaCl at pH 8.5 and then with 0.2M NaOAc [127-09-3]/0.5M NaCl at pH 4.0. A cryoppt. obtained from the citrate-treated whole blood was dissolved in an equiv. buffer and treated with Al(OH)3 for 3 min at 37.degree. to remove the vitamin K-dependent factors. After the removal of Al(OH)3 the supernatant was chromatographed on the treated Sepharose column and eluted with a linear gradient of 0.15-1.0M NaCl in 14 mM tri-Na citrate, and 2.14 mM CaCl2 at pH 6.85 and the factor VIIIR:vWP eluted at a salt concn. of 0.47M NaCl. The yield of factor VIIIR:vWP was 85%.

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=> file biosis; (factor viii c or f viii c or fviiic) and (amino acid# o
r salt# or arginine# or glycine#)
FILE 'BIOSIS' ENTERED AT 14:40:08 ON 06 NOV 92
COPYRIGHT (C) 1992 BIOSIS(R)

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 3 November 1992 (921103/ED)   BA9410  BR4310
CAS REGISTRY NUMBERS (R) LAST ADDED: 4 November 1992 (921104/UP)


        254314 FACTOR
         10798 VIII
        494280 C
           346 FACTOR VIII C
                 (FACTOR(W)VIII(W)C)
         95566 F
         10798 VIII
        494280 C
            76 F VIII C
                 (F(W)VIII(W)C)
            31 FVIIIC
        237621 AMINO
        669892 ACID#
        165324 AMINO ACID#
                 (AMINO(W)ACID#)
         64952 SALT#
         27687 ARGININE#
         35832 GLYCINE#
L6          36 (FACTOR VIII C OR F VIII C OR FVIIIC) AND (AMINO ACID# OR
               SALT# OR ARGININE# OR GLYCINE#)

=> s l6 and (polymer# or detergent#)
         19427 POLYMER#
         20099 DETERGENT#
L7           0 L6 AND (POLYMER# OR DETERGENT#)

=> s l6 and carbohydrate#
         57480 CARBOHYDRATE#
L8           0 L6 AND CARBOHYDRATE#

=> s l6 and pharmac?
        306091 PHARMAC?
L9           5 L6 AND PHARMAC?

=> file medline; s (factor viii c? or f viii c? or fviiic?) and (amino aci
d# or salt# or arginine# or glycine#)
FILE 'MEDLINE' ENTERED AT 14:42:58 ON 06 NOV 92
COPYRIGHT (C) 1992 U.S. National Library of Medicine  (NLM)

 FILE LAST UPDATED: 23 OCT 92 (921023/UP).  FILE COVERS 1972 TO DATE.

 SEE HELP CTAG FOR CHECK TAGS, HELP SUBHEADING FOR SUBHEADINGS
 AND HELP TREE FOR TREE NUMBER CATEGORY.

 +QLF/CT SHOWS YOU THE ALLOWABLE QUALIFIERS OF A TERM.


        190343 "FACTOR"
         11142 "VIII"
```

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TERM 'C?' EXCEEDED TRUNCATION LIMITS - SEARCH ENDED
You have entered a truncated stem which occurs in too many terms.
Make the stem longer and try again.  For example, if your original
term was 'degr?' to search for variations and the abbreviation for
'degradation', you could replace it with the expression '(degrdn OR
degrad?)'.  If your search term was numeric, e.g., 'C>5', reduce the
size of the range.

=> s l6
        190343 "FACTOR"
         11142 "VIII"
        309341 "C"
           269 FACTOR VIII C
                 ("FACTOR"(W)"VIII"(W)"C")
         60863 "F"
         11142 "VIII"
        309341 "C"
            83 F VIII C
                 ("F"(W)"VIII"(W)"C")
            24 FVIIIC
        188745 "AMINO"
        605440 ACID#
        165339 AMINO ACID#
                 ("AMINO"(W)ACID#)
         41704 SALT#
         21315 ARGININE#
         16803 GLYCINE#
L10         36 (FACTOR VIII C OR F VIII C OR FVIIIC) AND (AMINO ACID# OR
               SALT# OR ARGININE# OR GLYCINE#)

=> s l10 and (polymer# or detergent#)
        17356 POLYMER#
        16549 DETERGENT#
L11         0 L10 AND (POLYMER# OR DETERGENT#)

=> s l10 and pharmac?
       985620 PHARMAC?
L12        14 L10 AND PHARMAC?

=> dup rem l9,l12
FILE 'BIOSIS' ENTERED AT 15:12:50 ON 06 NOV 92
COPYRIGHT (C) 1992 BIOSIS(R)

FILE 'MEDLINE' ENTERED AT 15:12:50 ON 06 NOV 92
COPYRIGHT (C) 1992 U.S. National Library of Medicine  (NLM)
PROCESSING COMPLETED FOR L9
PROCESSING COMPLETED FOR L12
L13           17 DUP REM L9 L12 (2 DUPLICATES REMOVED)

=> d 1-17 an ti au so ab; file home

L13  1 OF 17  COPYRIGHT 1992 NLM
AN  91220290  MEDLINE
TI  The influence of infusions of 1-desamino-8-D-arginine
    vasopressin (DDAVP) in vivo on the anticoagulant effect of
    recombinant hirudin (CGP39393) in vitro.
AU  Ibbotson SH; Grant PJ; Kerry R; Findlay VS; Prentice CR
SO  Thromb Haemost, (1991 Jan 23)  65 (1)  64-6
    Journal code: VQ7  ISSN: 0340-6245
AB  Hirudin is a specific, potent inhibitor of thrombin that may be a
    valuable antithrombotic agent. The aim of this study was to
    investigate the hypothesis that the haemostatic effects of DDAVP
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counteract the coagulation defect induced by hirudin. The effect of DDAVP was studied in vivo on the anticoagulant action of recombinant hirudin (CGP39393) in vitro. Blood samples were taken at intervals from 10 normal volunteers infused with DDAVP. Factor VIII:C rose from (mean) 0.68 IU/ml before DDAVP to 2.19 and 2.16 IU/ml after 30 and 60 min infusion, respectively. Samples taken during DDAVP infusion showed a dose related decrease in the hirudin (0.5 and 1.0 microM) induced prolongation of the APTT, that occurred at FVIII:C concentrations of up to twice normal. At higher concentrations of hirudin no effect on the APTT occurred. These results demonstrate that DDAVP infusion elevates factor VIII:C levels with an associated significant reduction in the anticoagulant effect of hirudin in vitro.

L13 2 OF 17 COPYRIGHT 1992 NLM
AN 90132192 MEDLINE
TI Hematin: effects on hemostasis.
AU Green D; Ts'ao CH
SO J Lab Clin Med, (1990 Feb) 115 (2) 144-7 Ref: 22
Journal code: IVR ISSN: 0022-2143
AB Extensive studies performed over the past 6 years have shown that a degradation product of hematin produces a unique coagulopathy, characterized by thrombocytopenia with platelet degranulation, alteration in the function of numerous clotting and fibrinolytic proteins, and reversible changes in endothelial cells. With the use of degraded hematin, it can be demonstrated that platelet aggregation is stimulated, that platelet adhesion to endothelial cells is enhanced, that the dissociation of factor VIII:C from von Willebrand factor is inhibited, and that the binding of the factor VII/von Willebrand factor complex to platelets is impaired. Even freshly reconstituted solutions of sorbitol-stabilized hematin affect hemostasis and induce thrombophlebitis, presumably because of in vivo degradation of the hematin. Recently, a new formulation of hematin, heme arginate, has been shown to be extraordinarily stable and to have virtually no effects on coagulation. This review compares and summarizes the effects of these various hematin compounds on hemostasis.

L13 ANSWER 3 OF 17 COPYRIGHT 1992 BIOSIS
AN 88:181275 BIOSIS
TI SHORTENING OF BLEEDING TIME BY 1 DEAMINO-8-ARGININE VASOPRESSIN DDAVP IN THE ABSENCE OF PLATELET VON WILLEBRAND FACTOR IN GRAY PLATELET SYNDROME.
AU PFUELLER S L; HOWARD M A; WHITE J G; MENON C; BERRY E W
SO THROMB HAEMOSTASIS 58 (4). 1987. 1060-1063. CODEN: THHADQ ISSN: 0340-6245
AB The Gray platelet syndrome is a rare disorder characterised by the absence of platelet .alpha.-granules and their contents. We describe a new patient and the effects of infusions of 1-deamino-8-arginine vasopressin (DDAVP). The patient had a prolonged skin bleeding time and his platelets had reduced numbers of .alpha.-granules, increased vacuolation and reduced retention on glass beads. Platelet von Willebrand factor antigen (vWf: Ag) was undetectable and levels of platelet fibrinogen, .beta.-thromboglobulin, platelet factor 4 and thrombospondin were reduced. All tests of plasma coagulation factors were normal, including Factor VIII (F.VIII:C), vWf:Ag, ristocetin cofactor (R:CoF) and botrocetin cofactor. Platelet ATP, ADP, platelet albumin, surface membrane glycoproteins and 14C-serotonin uptake were also normal. Infusions of DDAVP increased plasma F. VIII:C, vWf:Ag and R:CoF and shortened the bleeding time on two occasions. This suggests that DDAVP shortens the bleeding

time by releasing vWf:Ag and/or other proteins from cellular storage sites other than the platelet.

L13 ANSWER 4 OF 17 COPYRIGHT 1992 BIOSIS DUPLICATE 1
AN 88:115492 BIOSIS
TI CONCENTRATED DDAVP FURTHER IMPROVEMENT IN THE MANAGEMENT OF MILD FACTOR VIII DEFICIENCIES.
AU GHIRARDINI A; MARIANI G; LACOPINO G; TIRINDELLI M C; SOLINAS S; MORETTI T
SO THROMB HAEMOSTASIS 58 (3). 1987. 896-898. CODEN: THHADQ ISSN: 0340-6245
AB This study was carried out to evaluate the pharmacological efficacy of a new concentrated 1 Deamino-(8-D-arginine)-vasopressin (DDAVP) preparation. Concentration DDAVP (C-DDAVP), (40 .mu.g/mL) was given subcutaneously (s.c.) in hemophilia and von Willebrand Disease (vWD), and the response was evaluated in terms of factor VIII/vWF (VIII/von Willebrand Factor) complex response. This response was also compared to that obtained using the currently available commercial preparation (4 .mu.g/mL) given either s.c. or intravenously (i.v.). The maximal f. VIII response after s.c. C-DDAVP was reached one hour after the injection (.hivin.x:3.5 times the resting values) with an average decline of 15% at two hours. The response to s.c. C-DDAVP in patients with hemophilia was slightly better than that obtained with the diluted brand, but the difference did not reach any statistical significance even when the schedules were compared in the same patients. In type I (platelet normal subtype) vWD, a higher response in terms of factor VIII:C increase in comparison with hemophiliacs was obtained. Both Ristocetin cofactor activity (RiCof) and bleeding time responded to this vasopressin analogue, when administered subcutaneously.

L13 ANSWER 5 OF 17 COPYRIGHT 1992 BIOSIS
AN 88:41062 BIOSIS
TI EFFECTS OF DDAVP AT COAGULATION AND FIBRINOLYTIC LEVELS DIFFERENT MECHANISMS OF ACTION AN EXPERIMENTAL STUDY IN THE DOG.
AU PINA-CABRAL J M; CUNHA-MONTEIRO A; SOUSA-DIAS M C; AGULAR-ANDRADE J
SO XITH INTERNATIONAL CONGRESS ON THROMBOSIS AND HAEMOSTASIS, BRUSSELS, BELGIUM, JULY 6-10, 1987. THROMB HAEMOSTASIS 58 (1). 1987. 366. CODEN: THHADQ ISSN: 0340-6245

L13 ANSWER 6 OF 17 COPYRIGHT 1992 BIOSIS DUPLICATE 2
AN 88:93645 BIOSIS
TI INHIBITOR TO FACTOR VIII IN A NONHEMOPHILIC PATIENT EVALUATION OF THE RESPONSE TO DDAVP AND THE IN-VITRO KINETICS OF FACTOR VIII A CASE REPORT.
AU CHISTOLINI A; GHIRARDINI A; TIRINDELLI M C; MORETTI T; MANCINI F; DI PAOLANTONIO T; MARIANI G
SO NOUV REV FR HEMATOL 29 (4). 1987. 221-224. CODEN: NRFHA4 ISSN: 0029-4810
AB We report a case of inhibitor to factor VIII in a non-haemophilic patient. Immunosuppressive therapy with azathioprine was started, but without any advantage. Evaluation of the kinetics of exogenous factor VIII in vitro showed a rapid but incomplete neutralization of factor VIII. Following s.c. 1-deamino-8-D-arginine vasopressin (DDAVP) administration, a large and prolonged increase in factor VIII:C and von Willebrand factor antigen occurred together with complete inhibitor saturation. Therefore DDAVP may represent an important tool in the management of the bleeding episodes in these patients and evaluation of its suitability in the management of these patients should be carried out.

L13 7 OF 17 COPYRIGHT 1992 NLM
AN 86208956 MEDLINE
TI Effects of arginine vasopressin (AVP) infusions on circulating concentrations of platelet AVP, factor VIII: C and von Willebrand factor.
AU Nussey SS; Bevan DH; Ang VT; Jenkins JS
SO Thromb Haemost, (1986 Feb 28) 55 (1) 34-6
Journal code: VQ7 ISSN: 0340-6245
AB To study the possible role of arginine vasopressin (AVP) in the control of haemostasis AVP infusions at 3 doses (0.1, 0.2 and 0.3 mU/kg/min) were performed in 6 male volunteers. Both plasma and platelet AVP concentrations rose in a dose-related manner. At doses of 0.2 and 0.3 mU/kg/min there was an increase in the plasma concentrations of both plasma Factor VIII and von Willebrand factor. The data support the hypothesis that AVP, by interacting with platelets and stimulating factor VIII and von Willebrand factor release, plays a role in the control of haemostasis.

L13 8 OF 17 COPYRIGHT 1992 NLM
AN 87176513 MEDLINE
TI Desmopressin (DDAVP) for treatment of disorders of hemostasis.
AU Mannucci PM
SO Prog Hemost Thromb, (1986) 8 19-45 Ref: 103
Journal code: Q1B ISSN: 0362-6350
AB At a time when the acquired immunodeficiency syndrome as well as hepatitis and other blood-borne diseases are a threat to patients with bleeding disorders who need treatment with blood products, it is rewarding to realize that a number of these patients can be safely and effectively treated with their own desmopressin-stimulated F.VIII:C and vWF. Desmopressin is clinically useful for treatment of patients with moderate and mild hemophilia. The limits of the clinical indications are established by the nature of the bleeding episode, the resting factor level, the level that must be achieved, and the length of time the level must be maintained to manage any given bleeding episode. In von Willebrand disease, desmopressin can be used more extensively to raise F.VIII:C levels than in classic hemophilia, because fewer of the patients have the severe form of the disease that is unresponsive to desmopressin. Increases in the level of F.VIII:C of about four times the resting value can be expected both in hemophilia and von Willebrand disease, but it must be borne in mind that the range of individual responses is large. Even though it is not easy to correct the prolonged bleeding time, particularly in patients with dysfunctional vWF, this drawback is of clinical relevance only in a minority of cases. A role for the use of desmopressin in acquired diseases of primary hemostasis has been proposed more recently, and experience is more limited than in congenital bleeding disorders. Uremia is probably the most firmly established indication because it has been shown that the bleeding time is often dramatically shortened by desmopressin, and hemorrhages can be stopped or prevented before surgical procedures. The indications for use of the compound in liver cirrhosis and congenital and acquired platelet dysfunctions are promising but much less established from a clinical standpoint. The bulk of available clinical experience is based on intravenous administration. Intranasal and subcutaneous administration have been successfully attempted and might be more convenient in selected circumstances, such as home treatment and the stimulation of blood donors to provide more abundant supplies of F.VIII:C and vWF. However, the responses after intranasal administration are less predictable and consistent than after intravenous administration.

Desmopressin has few troublesome side-effects. Mild facial flushing, a small increase in heart rate, and, more rarely, mild headache can occur transiently during infusion. Signs of hyponatremia or cerebral edema are extremely rare, providing that excessive fluid intake is avoided.(ABSTRACT TRUNCATED AT 400 WORDS)

L13 9 OF 17 COPYRIGHT 1992 NLM
AN 86131632 MEDLINE
TI Activation of porcine factor VIII:C by thrombin and factor Xa.
AU Lollar P; Knutson GJ; Fass DN
SO Biochemistry, (1985 Dec 31) 24 (27) 8056-64
Journal code: A0G ISSN: 0006-2960
AB The activation of porcine factor VIII:C by thrombin and by factor Xa was studied by a chromogenic substrate assay and by sodium dodecyl sulfate-polyacrylamide gel radioelectrophoresis of 125I-labeled factor VIII:C activation products. In the chromogenic assay, the kinetics of factor VIII:C dependent activation of factor X by factor IXa in the presence of calcium and phosphatidylserine/phosphatidylcholine vesicles were measured with N-benzoyl-L-isoleucyl-L-glutamylglycyl-L-arginine p-nitroanilide (S2222) as substrate. Substrate dependence of initial rates of the reaction at fixed factor IXa, factor VIII:C, lipid, and calcium obeyed Michaelis-Menten kinetics. At fixed factor IXa, factor X, lipid, and calcium the initial rates of the reaction varied linearly with lower factor VIII:C concentrations and plateaued at higher concentrations. The linear initial rate dependence formed the basis of a rapid, plasma-free assay of activated factor VIII:C. The activation of factor VIII:C by thrombin or factor Xa and the enzyme-independent rate of spontaneous inactivation were studied under conditions of excess enzyme. A model of the activation kinetics was developed and fit to the data by a nonlinear least-squares technique. From the model, the catalytic efficiencies (kcat/Km) of factor VIII:C activation by thrombin and factor Xa were 5.0 X 10(6) M-1 s-1 and 1.1 X 10(6) M-1 s-1, respectively. By comparison with published values of the catalytic efficiencies of several other coagulation enzymes for various substrates, both thrombin and factor Xa are efficient enzymes toward factor VIII:C.(ABSTRACT TRUNCATED AT 250 WORDS)

L13 10 OF 17 COPYRIGHT 1992 NLM
AN 85212779 MEDLINE
TI Absent factor VIII response to synthetic vasopressin analogue (DDAVP) in nephrogenic diabetes insipidus.
AU Kobrinsky NL; Doyle JJ; Israels ED; Winter JS; Cheang MS; Walker RD; Bishop AJ
SO Lancet, (1985 Jun 8) 1 (8441) 1293-4
Journal code: L0S ISSN: 0023-7507
AB To study the effect of 1-deamino-8D-arginine vasopressin (DDAVP) on the factor VIII response in nephrogenic diabetes insipidus (NDI), 0.30 microgram/kg DDAVP was given to 2 unrelated NDI patients, 3 obligate carriers, and 20 controls. Factor VIII coagulant activity (FVIIIC) and factor VIII related antigen (FVIIIR:Ag) responses were absent in both NDI patients and were decreased by approximately 50% in the carriers by comparison with controls. These results show that the vasopressin receptor defect in NDI is not confined to the kidney but is equally expressed in other tissues including the vascular endothelium and hepatic sinusoids, the

respective s[redacted]es of FVIIIR:Ag and FVIII[redacted] production. A decreased factor VIII response may help in identifying carriers in families at risk.

L13 ANSWER 11 OF 17 COPYRIGHT 1992 BIOSIS
AN 86:174581 BIOSIS
TI STUDIES ON THE EFFECT OF ADMINISTRATION OF 1 DESAMINO-8-D-ARGININE VASOPRESSIN IN PATIENTS WITH CEREBROVASCULAR OCCLUSIVE DISEASES FROM THE VIEWPOINT OF BLOOD COAGULATION-FIBRINOLYSIS IN VESSEL WALLS.
AU ARAI H; MIYAKAWA T; SAKURAGAWA N
SO ACTA MED BIOL 33 (3). 1985 (RECD. 1986). 151-162. CODEN: AMBNAS
ISSN: 0567-7734
AB To clarify the pathogenesis of cerebral thrombosis and to estimate the effectiveness of fibrinolytic treatment by administration of urokinase from the viewpoint of coagulation-fibrinolysis in vessel walls, changes of blood coagulation were investigated by intravenous administration of 1-deamino-8-D-arginine vasopressin (DDAVP) to 10 healthy volunteers and to 14 patients with cerebrovascular occlusive diseases. Results were as follows: (1) After the administration of DDAVP to normal controls, aPTT was shortened, PT was not changed, factor VIII:C and VIIIR:Ag were increased, euglobulin lysis time was shortened, plasminogen activator was increased, .alpha.2-plasmin inhibitor was decreased, and no changes of antithrombin III were observed. Increases in factor VIII:C and factor VIIIR:Ag were more prominent in the elder group. Coagulation-fibrinolytic changes were more marked after the administration of 8 .mu.g of DDAVP than those after the administration of 4 .mu.g DDAVP. (2) Activities of coagulation were higher and activities of fibrinolysis and release activity of plasminogen activator were lower in patients with severe cerebral arteriosclerosis than in patients with mild cerebral arteriosclerosis. Plasminogen activator was markedly increased in patients with mild cerebral arteriosclerosis, whereas a very slight increase was observed in patients with severe cerebral arteriosclerosis. (3) Plasminogen activator showed higher levels in the patients in whom urokinase therapy had been effective to recanalize the occluded cerebral artery than in those with no recanalization by urokinase therapy. One of the recanalized patients showed a remarkable increase in plasminogen activator after the administration of DDAVP.

L13 12 OF 17 COPYRIGHT 1992 NLM
AN 84204051 MEDLINE
TI Stabilization of thrombin-activated porcine factor VIII:C by factor IXa phospholipid.
AU Lollar P; Knutson GJ; Fass DN
SO Blood, (1984 Jun) 63 (6) 1303-8
Journal code: A8G ISSN: 0006-4971
AB The activation of porcine factor X by an enzymatic complex consisting of activated factor IX (factor IXa), thrombin-activated factor VIII:C (factor VIII:Ca), phospholipid vesicles, and calcium was studied in the presence of an irreversible inhibitor of factor Xa, 5-dimethylamino-naphthalene-1-sulfonyl-glutamyl-glycyl-arginyl- chloro met hyl ketone (DEGR -CK). The formation of factor Xa was measured continuously by monitoring the increase in solution fluorescence intensity that occurs upon formation of DEGR -factor Xa. Omission of any component from the enzymatic complex reduced the reaction rate to a negligible level. In the presence of fixed excess factor IXa, the velocity of factor X activation was linearly dependent on the concentration of

factor VIII:C, and thus, provided a plasma-free assay of factor VIII:C. Activation of factor VIII:C by 0.1 NIH U/ml thrombin in the presence of factor IXa, phospholipid vesicles, and calcium, followed at variable time intervals by the addition of factor X and DEGR -CK, was complete within 5 min, as judged by the fluorometric assay, and resulted in little or no loss of factor VIII:C activity over a period of 20 min; whereas, activation in the absence of either IXa or phospholipid vesicles decreased the half-life of factor VIII:C to approximately 5 min. Analysis of 125I-factor VIII:C-derived activation peptides by sodium dodecyl sulfate polyacrylamide gel radioelectrophoresis revealed identical results, regardless of whether factor IXa and/or phospholipid vesicles were included in the activation, suggesting that the lability of factor VIII:Ca is not due to a major alteration of its primary structure. We conclude that the activated porcine factor VIII:C molecule is stabilized markedly because of its interaction with factor IXa and phospholipid.

L13 13 OF 17 COPYRIGHT 1992 NLM
AN 85066481 MEDLINE
TI Structure-function relationships of human factor VIII complex studied by thioredoxin dependent disulfide reduction.
AU Hessel B; Jornvall H; Thorell L; Soderman S; Larsson U; Egberg N; Blomback B; Holmgren A
SO Thromb Res, (1984 Sep 15) 35 (6) 637-51
Journal code: VRN ISSN: 0049-3848
AB A highly purified, multimeric factor VIII complex composed of VIII: vWF and some factor VIII: C contained about 100 disulfides per subunit of Mr 260,000. Limited reduction of disulfide bonds in this complex by NADPH, thioredoxin reductase and thioredoxin leads to partial disaggregation of the multimeric VIII:vWF with concomitant loss of its platelet agglutinating activity in the presence of ristocetin, and with dissociation of factor VIII:C from the complex. During this event, no Mr 260,000 subunit of VIII:vWF is discernible. However, prolonged reduction results in the appearance of different multimers, and of some Mr 260,000 subunits. An N-terminal amino acid sequence for VIII:vWF was deduced. Two half-cystine residues in this sequence were shown to be involved in the reaction with thioredoxin. It appears possible that the thioredoxin system or other redox systems may play a role in regulation of factor VIII activities and of hemostatic processes in vivo.

L13 14 OF 17 COPYRIGHT 1992 NLM
AN 85021377 MEDLINE
TI Inhibition of activated porcine factor IX by dansyl-glutamyl-glycyl-arginyl-chloromethylketone.
AU Lollar P; Fass DN
SO Arch Biochem Biophys, (1984 Sep) 233 (2) 438-46
Journal code: 6SK ISSN: 0003-9861
AB Activated porcine Factor IX is irreversibly inhibited by an active site histidine-directed serine protease inhibitor, dansyl-glutamyl-glycyl-arginyl-chloromethylketone (DEGR-CK). The kinetics of inhibition are second order up to inhibitor concentrations of 10(-5) M. The apparent second-order rate constant (in 0.20 M NaCl, pH 8.0) is 1.7 X 10(4) M-1 min-1, which is considerably lower than values reported for Factor Xa, thrombin, plasmin, and kallikrein. Reaction of increasing concentrations of DEGR-CK with factor IXa, followed by analysis of residual enzymatic

activity, yields 1.2 mol DEGR-CK/mol protein, indicating 1:1 stoichiometry for the DEGR-CK/Factor IXa interaction. DEGR-Factor IXa is a potent anticoagulant in vitro. A concentration of 1 nM causes 50% inhibition of the ability of normal porcine-citrated plasma to correct either Factor VIII- or Factor IX-deficient plasmas (intrinsic pathway factors). In contrast, more than 100 nM DEGR-Factor IXa is required to cause 50% inhibition of Factor VII (extrinsic pathway) or Factor X (common pathway) assays. Activation of porcine Factor VIII:C by thrombin in the presence of DEGR-Factor IXa and phosphatidylcholine-phosphatidylserine vesicles reveals that DEGR-Factor IXa markedly stabilizes the spontaneous loss of Factor VIII:Ca activity as does unmodified Factor IXa [P. Lollar, G.J. Knutson, and D. N. Fass (1984) Blood 63, 1303-1308]. These results suggest that DEGR-Factor IXa incorporates into the intrinsic pathway Factor X-activator enzymatic complex, and also that stabilization of Factor VIII:Ca by this complex is independent of the active site of Factor IXa. Inhibition of Factor IXa by DEGR-CK results in the first reported irreversible active-site-modified derivative of this enzyme. DEGR-CK promises to be a useful reagent in the study of the Factor X activator complex. Conceivably, its specific anticoagulant properties could have future clinical benefit.

L13 15 OF 17 COPYRIGHT 1992 NLM
AN 84045584 MEDLINE
TI DDAVP: does the drug have a direct effect on the vessel wall?
AU Barnhart MI; Chen S; Lusher JM
SO Thromb Res, (1983 Jul 15) 31 (2) 239-53
Journal code: VRN ISSN: 0049-3848
AB Evidence is presented that 1-deamino-8-d-arginine vasopressin (DDAVP), a vasopressin analog, has a direct effect on isolated vessel segments. The most significant finding is increased platelet adhesion and spreading at injury sites. An isologous human umbilical vein perfusion model was used to compare effects of DDAVP with those of epinephrine or zero drug controls. Scanning electron microscopy, in conjunction with morphometry, permitted quantification of platelet adhesion to subendothelium exposed by minimal injury in the model. In addition, umbilical vein effluents were tested for levels of factor VIII moieties (F VIII:C , F VIII:Rag, F VIII:RCof) and the prostanoids, 6 keto PGF1 alpha (stable metabolite of prostacyclin) and TXB2 (stable metabolite of thromboxane A2. Only F VIII:C from DDAVP treated segments was significantly (p less than 0.01) changed from controls.

L13 16 OF 17 COPYRIGHT 1992 NLM
AN 82109216 MEDLINE
TI Accumulative effect of DDAVP and heparin in increasing plasma factor VIII levels.
AU Rock G; Palmer DS
SO Vox Sang, (1981) 41 (1) 56-60
Journal code: XLI ISSN: 0042-9007
AB DDAVP (1-desaminocysteine-(8-D-arginine)-vasopressin) produces a marked increase in plasma factor VIII procoagulant (F VIII:C) levels. Previously, we have reported that blood collected into heparin rather than into CPD anticoagulant results in higher starting levels of plasma F VIII:C activity. We therefore wished to determine whether the effects of these two agents were accumulative and whether they would result in any difference in the relative molecular distribution of F VIII:C. Blood was collected into CPD or heparin immediately before and 15 min after an

intravenous dose of 0.2 micrograms/kg body weight of DDAVP. Pre-stimulation factor VIII levels were approximately 36% higher in heparinized plasma than in CPD plasma. Following DDAVP stimulation, the final factor VIII activity was increased 3.9-fold when either of the anticoagulants was used, with the heparin sample maintaining a 37% increase over the CPD sample. Column chromatography on Sepharose CL-6B of pre- and post-DDAVP plasma samples collected into either heparin or CPD indicated that there was no change in the relative distribution of the high and low molecular weight forms of F VIII:C. The heparinized sample showed the typical distribution of approximately 60% F VIII: C at void volume (Vo) and 40% at 2.3 Vo, suggesting that DDAVP-stimulated increases of plasma F VIII: C are equally distributed between the carrier and non-carrier associated F VIII:C activities.

L13 17 OF 17 COPYRIGHT 1992 NLM
AN 76271687 MEDLINE
TI The dissociation of factor VIII by reducing agents, high salt concentration and affinity chromatography.
AU Peake IR; Bloom AL
SO Thromb Haemost, (1976 Feb 29) 35 (1) 191-201
Journal code: VQ7
AB Incubation of a factor VIII-rich fraction of plasma with a high concentration of salt confirmed the production of both high (HMW) and low (LMW) molecular weight factor VIII clotting activity (FVIIIC) as determined by agarose gel filtration but with considerable overlap. The electrophoretic mobility of factor VIII related protein (FVIIIRP) detected by precipitating rabbit antiserum was not affected by this treatment and LMW FVIIIC devoid of FVIIIRP was apparently produced. At low concentration the reducing agent dithiothreitol (DTT) altered the electrophoretic mobility of FVIIIRP. At higher concentrations it altered both its mobility and antigenicity and an LMW FVIIIRP was produced. Contrary to the findings of other workers no LMW FVIIIC devoid of FVIIIRP was produced. In further studies factor VIII-rich plasma fraction was treated with sepharose beads to which had been coupled a non-coagulation inhibitory precipitating rabbit antibody to FVIIIRP. Both FVIIIRP and FVIIIC were taken up by the beads but after elution with 1.5 M NaCl, FVIIIC of LMW and devoid of FVIIIRP was selectively removed. Antisera raised to LMW FVIIIC produced with 1.5 M NaCl either by the gel filtration or affinity chromatography methods inhibited FVIIIC and precipitated with HMW factor VIII-rich fractions. The results were consistent with the possibility that factor VIII clotting activity and FVIIIRP exist in plasma as a non-covalently bound complex.

FILE 'HOME' ENTERED AT 15:13:30 ON 06 NOV 92

?t 3/3,ab/1

3/3,AB/1 (Item 1 from file: 434)
11161023 Genuine Article#: GL999 Number of References: 0
(NO REFS KEYED)
Title: ADSORPTION OF HUMAN-ANTIBODIES TO FACTOR-VIII-C TO INSOLUBLE MODIFIED POLYSTYRENE FROM PLASMA
Author(s): BOISSONVIDAL C; MESSAIKEH H; JOZEFONVICZ J
Corporate Source: UNIV PARIS 13,CTR SCI & POLYTECH,RECH MACROMOLEC LAB,CNRS,D0502,AVE JB CLEMENT/F-93430 VILLETANEUSE//FRANCE/
Journal: JOURNAL OF MATERIALS SCIENCE-MATERIALS IN MEDICINE, 1991, V2, N4, P193-196
Language: ENGLISH Document Type: ARTICLE
Abstract: Human procoagulant factor VIII (FVIII:C), is a protein that participates in the cascade of blood coagulation. It is absent or defective in haemophiliac A patients. Furthermore, about 5%-10% of severely affected patients who have received FVIII concentrate as treatment, are developing antibodies which neutralize FVIII:C. Some functional polymers with suitable chemical substituents fixed on to their macromolecular chain might be used in extracorporeal circulation to reduce the concentration of these antibodies. For this purpose, insoluble polystyrenes bearing sulphonate and various amino acid sulphamide groups have been synthesized. The affinity constants for the anti VIII:C and the IgG were determined in purified solution, K(anti VIII:C) = 10(8)-10(9) \ mol-1 and K(IgG) = 10(5) \ mol-1. The in vitro removal of the anti VIII:C from haemophiliac patient plasma with a high level of antibodies, was tested on various polystyrene-derivative resins. This has led to the selection of active polymers, such as polystyrene substituted by glutamic dimethyl ester acid and/or by hydroxyproline.
?b 76,73,149,144,434

09nov92 10:08:38 User219783 Session D114.3

Touzeau
864610

09nov92 09:58:03 User219783 Session D114.2

SYSTEM:OS - DIALOG OneSearch
File 73:EMBASE (EXCERPTA MEDICA) 74-92/ISS44
(COPR. ESP BV/EM 1992)
**FILE 73: Truncate EMTREE Codes (e.g. DC=C1.120?) for complete
**retrieval. See HELP NEWS 72 for new country codes and countries.
File 144:PASCAL 1973 - 1992 OCT
(C. INIST/CNRS 1992)
**FILE144: Backfile has been added. Limit problem: see ?news144
File 74:INTERNATIONAL PHARMACEUTICAL ABS. 70-92/DEC
(COPR. ASHP 1992)
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New rates can be viewed on September 1 by entering ?rates74.
File 434:SCISEARCH 1974 - 9210W4
(COPR. ISI INC. 1992)
**FILE434: Contains complete, merged SciSearch file
**Includes abstracts as of 1991

Set	Items	Description

?s factor(w)viii(w)c or f(w)viii(w)c or fviiic

	601023	FACTOR
	31586	VIII
	1125688	C
	543	FACTOR(W)VIII(W)C
	194866	F
	31586	VIII
	1125688	C
	109	F(W)VIII(W)C
	36	FVIIIC
S1	668	FACTOR(W)VIII(W)C OR F(W)VIII(W)C OR FVIIIC

?s s1 and (amino(w)acid? ? or arginine? ? or glycine? ? or salt? ?)

	668	S1
	346313	AMINO
	1645777	ACID? ?
	251697	AMINO(W)ACID? ?
	45456	ARGININE? ?
	51481	GLYCINE? ?
	152834	SALT? ?
S2	41	S1 AND (AMINO(W)ACID? ? OR ARGININE? ? OR GLYCINE? ? OR SALT? ?)

?s s2 and (polymer? ? or detergent? ?)

Processing

	41	S2
	368498	POLYMER? ?
	28343	DETERGENT? ?

```
=> s FFactorVVIIIconcentrate$
        183024 FACTOR
         71814 VIII
        183902 CONCENTRATE?
L1         124 FACTOR VIII CONCENTRATE?
                 (FACTOR(W)VIII(W)CONCENTRATE?)

=> s highly purified
        347255 HIGHLY
         93588 PURIFIED
L2        3474 HIGHLY PURIFIED
                 (HIGHLY(W)PURIFIED)

=> s detergentdeterge
L3       21800 DETERGENT

=> s 530/383/ccls or 514/12/ccls or 514/21/ccls
           189 530/383/CCLS
           770 514/12/CCLS
           982 514/21/CCLS
L4        1671 530/383/CCLS OR 514/12/CCLS OR 514/21/CCLS

=> s l1 and l2 and l3 and l4
L5           3 L1 AND L2 AND L3 AND L4

=> d l5 1-3

1.  5,300,433, Apr. 5, 1994, Methods for the inactivation of viruses in
viral-contaminated pharmaceutical compositions; Michael E. Hrinda, et
al., 435/238; 424/94.3, 530; 435/236; **514/21**; 530/380, 381, 384
[IMAGE AVAILABLE]

2.  5,118,795, Jun. 2, 1992, Sequential heat treatment of blood-clotting
factor products; Alan I. Rubinstein, **530/383**, 380 [IMAGE AVAILABLE]

3.  4,963,657, Oct. 16, 1990, Monoclonal antibodies to the light chain
region of human factor XII and methods of preparing and using the same;
Robin A. Pixley, 530/388.25; 424/85.8; 435/5, 240.27; 530/380, 382,
**383**, 413, 415, 417 [IMAGE AVAILABLE]

=> s Factor VIII and amino acid and detergent and l4
        183024 FACTOR
         71814 VIII
           665 FACTOR VIII
                 (FACTOR(W)VIII)
        111703 AMINO
        335079 ACID
         20003 AMINO ACID
                 (AMINO(W)ACID)
         21800 DETERGENT
L6           8 FACTOR VIII AND AMINO ACID AND DETERGENT AND L4

=> s l6 and polymer
        162203 POLYMER
L7           5 L6 AND POLYMER

=> d l7 1-5

1.  5,317,092, May 31, 1994, Protein purification method; Jan Markussen,
```

2. 5,047,249, Sep. 10, 1991, Compositions and methods for treating skin conditions and promoting wound healing; John Rothman, et al., 424/543, 529, 530; 514/2, **21**, 842, 859, 861, 863, 886, 887 [IMAGE AVAILABLE]

3. 4,952,675, Aug. 28, 1990, Method for purifying antihemophilic factor; Rita W. Mathews, et al., **530/383**; 210/656; 424/530; 514/822; 530/384, 412, 413 [IMAGE AVAILABLE]

4. 4,847,362, Jul. 11, 1989, Method for purifying antihemophilic factor; Rita W. Mathews, et al., **530/383**; 210/656; 514/822; 530/384, 412, 415 [IMAGE AVAILABLE]

5. 4,743,680, May 10, 1988, Method for purifying antihemophilic factor; Rita W. Mathews, et al., **530/383**; 210/656; 514/822; 530/384, 412, 413, 415 [IMAGE AVAILABLE]

=>

```
ENTER LOGIC EXPRESSION, QUERY NAME, OR (END):factor viii
         164815 FACTOR
          65543 VIII
L1          521 FACTOR VIII
                  (FACTOR(W)VIII)

=> s amino(w)acid
          99104 AMINO
         302538 ACID
L2        16391 AMINO(W)ACID

=> s detergent
L3        19551 DETERGENT

=> s l1 qndd l2 and l3
MISSING OPERATOR 'L1 ANDD'

=> s l1 and l2 and l3
L4            20 L1 AND L2 AND L3

=> s l4 and polymer
         142969 POLYMER
L5            8 L4 AND POLYMER

=> d l5 1-8

1.  5,166,133, Nov. 24, 1992, Method for inhibing adhesion of white blood
cells to endothelial cells; L. L. Houston, et al., 514/8 [IMAGE
AVAILABLE]

2.  5,063,081, Nov. 5, 1991, Method of manufacturing a plurality of
uniform microfabricated sensing devices having an immobilized ligand
receptor; Stephen N. Cozzette, et al., 427/2; 204/153.12, 403, 415, 418;
422/57; 427/407.1, 414; 435/7.1 [IMAGE AVAILABLE]

3.  5,047,249, Sep. 10, 1991, Compositions and methods for treating skin
conditions and promoting wound healing; John Rothman, et al., 424/543,
529, 530; 514/2, 21, 842, 859, 861, 863, 886, 887 [IMAGE AVAILABLE]

4.  4,994,439, Feb. 19, 1991, Transmembrane formulations for drug
administration; John P. Longenecker, et al., 514/3; 424/45; 514/2, 171,
808, 922, 947, 958, 975 [IMAGE AVAILABLE]

5.  4,952,675, Aug. 28, 1990, Method for purifying antihemophilic factor;
Rita W. Mathews, et al., 530/383; 210/656; 424/530; 514/822; 530/384,
412, 413 [IMAGE AVAILABLE]

6.  4,847,362, Jul. 11, 1989, Method for purifying antihemophilic factor;
Rita W. Mathews, et al., 530/383; 210/656; 514/822; 530/384, 412, 415

7.  4,743,680, May 10, 1988, Method for purifying antihemophilic factor;
Rita W. Mathews, et al., 530/383; 210/656; 514/822; 530/384, 412, 413,
415
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8. 4,737,544, Apr. 12, [illegible]88, Biospecific polymers; S. Howard McCain, et al., 424/443, 409, 422; [illegible]7/2; 525/54.1; 604/5, 6

=> s l4 and glycine
15062 GLYCINE
L6 9 L4 AND GLYCINE

=> d 16 1-9

1. 5,112,755, May 12, 1992, Preparation of functional human urokinase proteins; Herbert L. Heyneker, et al., 435/215, 172.3, 240.2, 252.33, 320.1; 536/27 [IMAGE AVAILABLE]

2. 4,994,439, Feb. 19, 1991, Transmembrane formulations for drug administration; John P. Longenecker, et al., 514/3; 424/45; 514/2, 171, 808, 922, 947, 958, 975 [IMAGE AVAILABLE]

3. 4,960,700, Oct. 2, 1990, Compositions and methods for the synthesis and assay of a mammalian enkephalinase; Bernard Malfroy-Camine, et al., 435/172.3, 212, 219, 240.2, 252.33 [IMAGE AVAILABLE]

4. 4,957,910, Sep. 18, 1990, Method and composition for the treatment and prevention of viral infections; Peter M. Sutton, et al., 514/182, 934 [IMAGE AVAILABLE]

5. 4,952,675, Aug. 28, 1990, Method for purifying antihemophilic factor; Rita W. Mathews, et al., 530/383; 210/656; 424/530; 514/822; 530/384, 412, 413 [IMAGE AVAILABLE]

6. 4,870,160, Sep. 26, 1989, Polypeptides with laminin activity; Aristidis S. Charonis, et al., 530/326; 623/1, 2, 6, 11, 15, 23, 66; 930/10, DIG.811

7. 4,847,362, Jul. 11, 1989, Method for purifying antihemophilic factor; Rita W. Mathews, et al., 530/383; 210/656; 514/822; 530/384, 412, 415

8. 4,816,397, Mar. 28, 1989, Multichain polypeptides or proteins and processes for their production; Michael A. Boss, et al., 435/69.6, 172.3, 243, 252.31, 252.33, 255, 320.1; 930/10

9. 4,743,680, May 10, 1988, Method for purifying antihemophilic factor; Rita W. Mathews, et al., 530/383; 210/656; 514/822; 530/384, 412, 413, 415

=> s 4743680/pn glycine
MISSING OPERATOR

=> d 4743680/pn glycine
'4743680' MUST END IN '/Q', '/A', OR '/L'

=>

```
* * * * * * *
=> s 514/12/ccls or 514/21/ccls or 530/383/ccls
          1071 514/12/CCLS
          1164 514/21/CCLS
           220 530/383/CCLS
L1        2090 514/12/CCLS OR 514/21/CCLS OR 530/383/CCLS
=> s factor VIII
        208129 FACTOR
         79225 VIII
L2         823 FACTOR VIII
                 (FACTOR(W)VIII)
=> s l1 and l2
L3         240 L1 AND L2
=> s purif?
L4      142914 PURIF?
=> s l4 and l3
L5         204 L4 AND L3
=> s detergent
L6       24779 DETERGENT
=> s l5 and l6
L7           42 L5 AND L6
=> s amino(w(acid
MISSING OPERATOR 'AMINO(W'
=> s amino(w)acid
        127082 AMINO
        374318 ACID

L8       24649 AMINO(W)ACID
=> s l7 and l8
L9           15 L7 AND L8
=> s polymer
L10     186385 POLYMER
=> s l9 and l10
L11           6 L9 AND L10
=> d l11 1-6

1.  5,445,958, Aug. 29, 1995, Process for **purifying** blood clotting
factors; Peter A. Feldman, 435/214; 530/381, 382, **383**, 384, 412, 416
[IMAGE AVAILABLE]

2.  5,317,092, May 31, 1994, Protein **purification** method; Jan
Markussen, 530/413; 435/7.2; 530/345, 351, 381, **383**, 399, 412 [IMAGE
AVAILABLE]

3.  5,047,249, Sep. 10, 1991, Compositions and methods for treating skin
conditions and promoting wound healing; John Rothman, et al., 424/543,
529, 530; 514/2, **21**, 842, 859, 861, 863, 886, 887 [IMAGE AVAILABLE]
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4. 4,952,675, Aug. 28, 1990, Method for **purifying** antihemophilic factor; Rita W. Mathews, et al., **530/383**; 210/656; 424/530; 514/822; 530/384, 412, 413 [IMAGE AVAILABLE]

5. 4,847,362, Jul. 11, 1989, Method for **purifying** antihemophilic factor; Rita W. Mathews, et al., **530/383**; 210/656; 514/822; 530/384, 412, 415 [IMAGE AVAILABLE]

6. 4,743,680, May 10, 1988, Method for **purifying** antihemophilic factor; Rita W. Mathews, et al., **530/383**; 210/656; 514/822; 530/384, 412, 413, 415 [IMAGE AVAILABLE]
=>